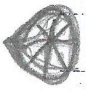
②

Polycystic ovarian Syndrome. (PCOS)

It affects ≈ 6% to 8% (1 of 15) women of reproductive age.

: It's Considered the leading cause of anovulatory infertility and the most Common endocrine abnormality for this age group.



ليه endocrine؟ علشان زى ما هنشوف فى الـ pathophysiology من اهم اسباب حدوث المرض هو زيادة فى افراز الـ GnRH. وبالتالى المشكلة مشكلة هرمونات ← تبقى على طول endocrine disorder.

المرض ده اتعرف بكذا اسم من خلال السنين اللى فاتت من ساعة ما اكتشفوه زى:

- Stein-leventhal syndrome وده اسم العلماء اللى اكتشفوه
- Polycystic ovary
- Polycystic ovarian disease
- Hyperandrogenic Chronic anovulatory syndrome.
- Functional ovarian hyperandrogenism.

ماتتعبوش الاسماء. لما ناخد كل حاجة عن المرض هتفهموا سبب كل اسم.

تعالوا دلوقتى نشوف ايه اللى بيخلى المرض يحصل وايه الحاجات المسئولة عن الاصابة ...

كل ده متجمع فى الـ pathophysiology

والجزء اللى جاى ده لو فهمناه باقى المحاضرة هيبقى مبنى عليه وسهل

Pathophysiology of PCOS

It's a complex pathophysiology. A genetic basis for PCOS has been postulated but its mode of transmission is unclear

The primary defect is unknown but it was found that 3 potential mechanism (acting alone or synergisticly) create the characteristic clinical presentation.

كل ده رغي ، اللي عايزينه تطلع بيه ان السبب ال ١° مش معروف بس
فيه ٣ حاجات اساسية هي المسئولة عن ظهور الاعراض الخاصة
بالمرض. والحاجات دي مش شرط تبقى كلها موجوده او بس ١ او ٢ منهم.
ودول بقى هناخدهم بالتفصيل

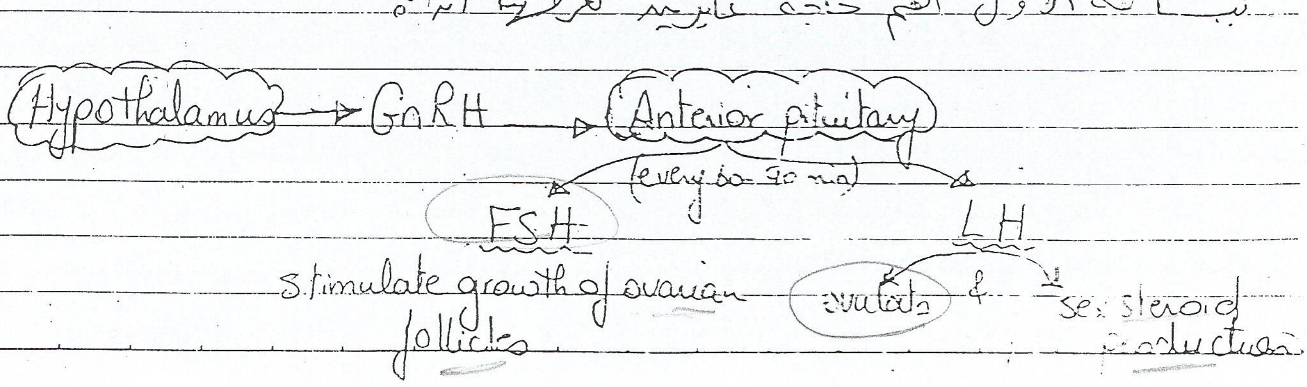
They are :

① Gonadotropin secretion
② Excess androgen production
③ Insulin

1] Gonadotropin secretion :

في الاول تعالوا نفهم في ال normal بيحصل ايه والهرمونات الاساسية
ايه. الكلام ده قلناه قبل كده في محاضرة ال infertility بس هنقوله
تاني واحط نفس الرسمة علشان الدكتورة شرحت عليها وهي بتشرح
المذاكرة

بس في الاول اهم حاجة عايزينك تعرفها ايه ؟


Hypothalamus
GnRH
Anterior pituitary
(every 60-90 min)
FSH
LH
stimulate growth of ovarian follicles
ovulation
&
sex steroid production

تعالوا بقى نقول كلام الكتاب :

* In normal menstrual cycles: (تابعوا الكلام مع الرسمة الصفحة الجاية)

- Ovulation occurs when hypothalamus produces Gonadotropin releasing hormone (Gn-RH) a neurohormone that regulates the release of FSH & LH from the anterior pituitary in a pulsatile fashion.

  - FSH : stimulate growth of ovarian follicles (∴ FSH is ↑ in follicular phase)
  - LH : stimulate ovulation (rupture of mature follicle & release of ovum)
    Sex steroid production.
    (∴ LH is high in ovulatory phase)

- Estrogen levels rise during the late part of follicular phase generating the LH surge → resulting in ovulation.

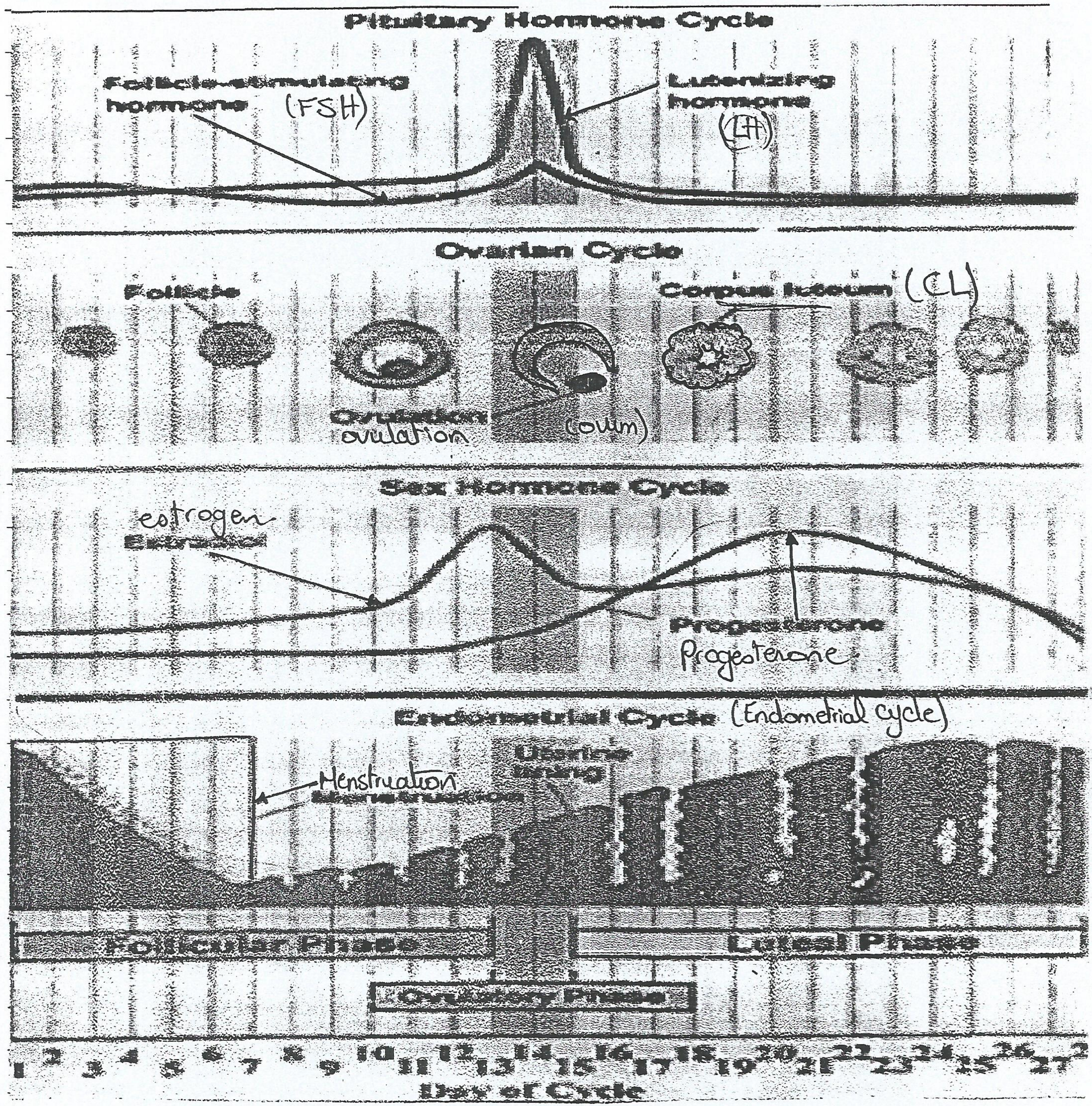
يعني في اواخر ال follicular phase لما بيكون فيه follicle واحده بقت dominant وخلاص جاهزة تعمل rupture ال estrogen بيعلى اوي في الدم وده بيؤدي الى علو ال LH → ovulation
→ called LH surge

- During the luteal phase (that follows ovulation) progesterone is synthesized & secreted → necessary for implantation of an embryo if pregnancy occured.

if pregnancy didn't occur progesterone decrease & menstruation occur

واظن انا عارفين الزبدة : ان ال progesterone بيعمل thickening لل endometrium استعدادا لل implantation بتاع ال embryo. انما لو محصلش → ال prog. هيقل ويحصل menstruation.

⑤ ~~14~~


Pituitary Hormone Cycle
Follicle-stimulating hormone (FSH)
Lutenizing hormone (LH)
Ovarian Cycle
Follicle
Corpus luteum (CL)
Ovulation
ovulation
(ovum)
Sex Hormone Cycle
estrogen
Estradiol
Progesterone
Progesterone
Endometrial Cycle (Endometrial cycle)
Uterine lining
Menstruation
Menstruation
Follicular Phase
Luteal Phase
Ovulatory Phase
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 15 26 27 2
Day of Cycle

كل ده طبعا في الطبيعي، تعالوا نشوف بقا ال PCOS ايه اللي بيحصل

* In PCOS:

↑↑ frequency of GnRH release stimulates leading to → increase of LH pulse frequency & amplitude.

while FSH remain normal or even ↓

- the development of a dominant follicle doesn't occur because LH secretion occurs too early in the cycle.

∴ A woman is left with several immature follicles and usually will not ovulate.

- A woman with this abnormality doesn't enter luteal phase

∴ Progesteron will not be sufficiently produced

∴ high Estrogen levels (from the follicular phase) will remain unopposed by progesteron.

غير معترض بحدود

Unopposed estrogen leads to endometrial hyperplasia & increase the risk of endometrial cancer.

- Increased LH stimulation will lead to increased steroidogenesis in ovary leading to excess androgen production.

(هنشرح آخر جملة دي في العنوان اللي جاي)

نجيبوا الفكره ببساطة ان معدل ال GnRH بيزيد ده بيؤدي الى زياده ال LH ونقص ال FSH واحنا عارفين ان ال FSH ده مسئول عن نضج ال follicles وال LH مسئول عن ال ovulation بس الحاجات دي متحصل فقط لو ال LH & FSH اتفرزوا في الوقت الصح بالكمية الصح.

↑LH FSH↓

وده في حالة ال PCOS مش بيحصل. فتكون ايه النتيجة ؟

النتيجة بتكون ان ال follicles بتكبر شوية بس مش للآخر وتفضل الست بكذا immature follicles و في اغلب الاحيان ده بيؤدي ان مايحصلش ovulation

المشكلة بقى كمان ان لو محصلش ال ovulation ال Corpus luteum مش هيطلع ودة هو اللي بيفرز ال progesterone في ال luteal phase وال progesterone ده المعروف في الطبيعي يعارض (oppose) ال estrogen اللي كان عالي في اواخر ال follicular phase وبيوطيه تاني

لما ما حصلش ovulation. كل ده مش هيحصل ↓

∴ estrogen remain unopposed → endometrial hyperplasia

endometrial cancer ←

- احنا كمان قلنا ان زيادة ال GnRH بيزود ال LH وال LH ده بيحفز خلايا معينة في ال ovaries (Theca cells) انها تفرز ال androgens و هنعرف بعد كده ان زيادة ال androgens هي السبب في كتير من الاعراض.

كده خلصنا اول نقطة في ال pathophysiology تعالوا نشوف التانية.

2] Excess androgen production:

هكتب كلام الكتاب الاول وبعدين ارسم واشرح .

- Androgen production occurs in the Theca cell of the ovary to facilitate: - follicular growth
  & - Estradiol synthesois in the granullosa cells.

ده من الوضع الطبيعي .

- In women with PCOS, hypersecretion of LH and insulin (explained Later) increase the production of androgens, Causing a state of hyperandrogenism → ، وهتعرف هتظهر من شكل ايه بعدين .

Normally
- Androstenedione is synthesized in theca cells and then:

  - Converted to testosterone (in theca cells)

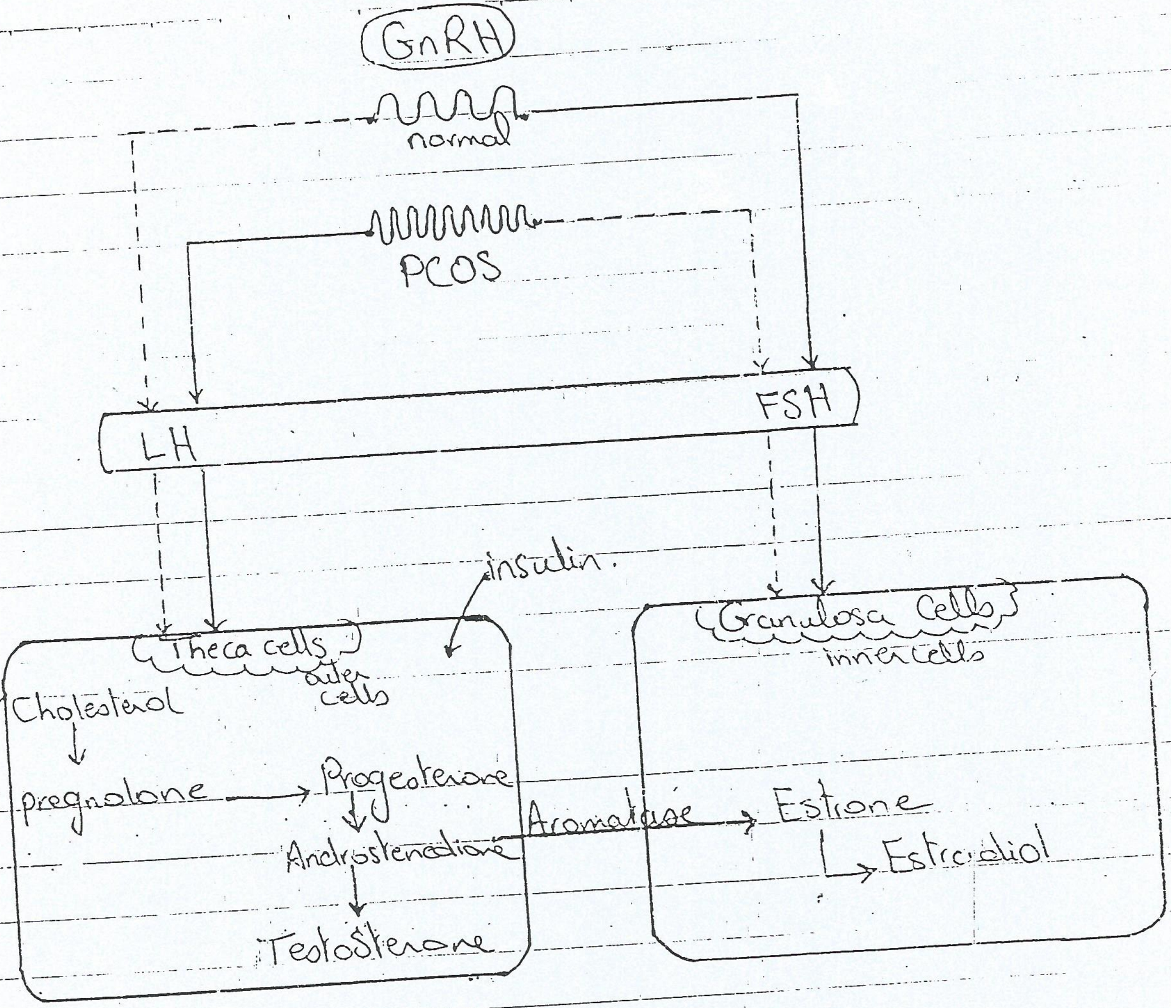
  or

  - Aromatized by aromatase enzyme to form estrone.

- In women with PCOS Theca cells are more efficient at the Conversion to Testosterone than normal cells.

Also a similar pathway of steroid synthesois occurs in the adrenal cortex, which is exacerbated in case of hyperandrogenism or hyperinsulinic state.

ده كلام الكتاب اللي الدكتورة قالته تعالوا نشوف الرسمة والشرح . الرسمة هتفهمكم حلو .


GnRH
normal
PCOS
LH
FSH
insulin.
Theca cells
outer cells
Cholesterol
pregnolone
Progesterone
Androstenedione
Testosterone
Aromatase
Granulosa cells
inner cells
Estrone
Estradiol

الفكره ببساطة زي ما انتم شايفينه في الرسمة : ال Theca cells
وال granulosa cells دول هي ال cells المحاوطة ال follicle
يعني ال follicle اللي بتكبر جوه ال ovary دي بتكون متكونة من
خلايا من جوه اسمها Granulosa وخلايا من بره اسمها Theca

كل نوع منهم بيطلع حاجة وبيتحفز بحاجة.

Theca cells (Outer cells)
- stimulated by LH
- secrete Testosterone.

Granulosa Cells (inner cells)
- stimulated by FSH
- secrete estrogen.

الخطوط العادية والمتقطعة دي بتدل على كمية ال stimulats & secretion

بيقى زي ما احنا عارفين ان في حالة ال PCOS ال GnRH بيبان
فبيحفز انتاج ال LH اكتر من ال FSH
لما ال LH يزيد ← تحفيز للـ theca cells هيزيد ← وبالتالي
ال testosterone هيزيد، وفي نفس الوقت ال FSH will decrease
فال estrogen مش هيتصنع بنفس القدار.

بس الدكتورة قالت ان لما ال testosterone يزيد هيحصله
Peripheral aromatization → ↑↑ estrogen.

- معلومة اخيرة : ال insulin كمان بيحفز ال Theca cells

- كمان وجدوا ان زيادة ال insulin & testosterone بيحفز ال pathway
بتاع ال androgen synthesis في ال adrenal cortex

كل ده بيعمل hyperandrogenism ودي ال clinical picture
بتاعتها هنعرفها في ال Signs & symptoms

ها ؟ فهمتم ولا ايه ؟؟ يارب تكونوا فهمتم ... لو لأ ابقوا
اسالونا واحنا نجاوب على طول.

تعالوا دلوقتي نتكلم عن آخر نقطة في ال pathophysiology.

3] Insulin:

- Women with PCOS experience an increased risk of insulin resistance with compensatory hyperinsulinemia.

- Insulin resistance is associated with reproductive & metabolic abnormalities.

- Insulin resistance occur in both obese & non obese women.

- The insulin resistance has been shown to be a selective, tissue-specific process
يعني بتختلف نوع ال tissue.

where: - insulin sensitivity increase in the ovarian androgenic pathway → causing hyperandrogenism.

but - insulin resistance is seen in other tissues involved with Carbohydrate metabolism specifically in fat & muscle

يعني ال insulin sensitivity بتاعة ال receptors بتزيد في ال ovaries
وبتقل في باقي ال tissues خاصة العضلات وال Fat.

وده بيؤدي الى
زيادة في ال androgen synthesis
Carbohydrate metabolic abnormalities

وللناس اللي ماتعرفش يعني ايه insulin resistance. ده معناه انه فيه insulin في الدم لكن الخلايا مش حاسه بيه. وبالتالي الخلايا بتبقى مش عارفة تستعمل ال glucose اللي في الدم فالجسم بيحس بنقصان في ال insulin فيزوده عكلنا ... ويعمل hyperinsulinemia

تعالوا نشوف تأثير ال insulin العالي ايه، وازاي بيشارك في ظهور اعراض ال PCOS

- In PCOS, insulin has both direct & indirect roles:

* **Direct role in:**

1) **Ovary**: . insulin acts alone or synergistically with LH to increase androgen production in theca cells.
   . Atresia is promoted.
2) **Liver**: insulin inhibits synthesis of sex-hormone binding globulin (SHBG) ....

∴ hyperinsulinemia is a major contributor (plays a major role) in both hyperandrogenism & hyperandrogenemia in PCOS

* **Indirect role:**

insulin may enhance the amplitude of LH pulses.

طيب يعني ايه atresia وايه هو ال SHBG ده؟

* Atresia: معناها ان ال follicle تضمر وما تكبرش.
واحنا كنا قلنا قبل كده ان قلة ال FSH بيودي الى ان ال follicles ما تكبرش. يبقى دلوقتي اللي بيساعد على العملية دي برضه هو زيادة ال insulin.

* SHBG: it's a key protein that binds to testosterone in plasma. so the decrease of this protein lead to increase in the free fraction of testosterone in blood ∴ more testosterone is available for biologic activity

وده اللي بيودي الى ظهور اعراض ذكورية زي ما هنشوف بعد شوية

كده خلصنا الpathophysiology. تعالوا نشوف الClinical characteristics

Clinical Characteristics

لازم الاول نفهم ان الاعراض دي مش شرط كلها تظهر ، في منها common زي اول ٣ هنشوفهم دلوقتي بس زي ما قلنا في الاول ان ده syndrome ومعنى كدة انه مش كل ست عندها PCOS بيبقى عندها نفس الاعراض

طيب امال ازاي هنحكم ونشخص المرض ؟ هنعرف من العنوان اللي بعد ده.

نشوف دلوقتي الاعراض (اول ٣ دول اشهر ٣)

1) Hirsutism: most common 60-70% of women with PCOS.

2) Acne: 15-25% of PCOS women.

3) Alopecia: 5% of PCOS women.

4) Ovulatory dysfunction: $\underbrace{\text{oligo-ovulation or anovulation}}$

presented clinically as irregularity in menstrual Cycles.

60-85% of women with PCOS + oligovulation have menstrual dysfunction, usually
- oligomenorrhea (less frequent menstrual cycles)
- or amenorrhea. (no menstrual cycles)

n.b: an increased $\frac{LH}{FSH}$ ratio > 2 or 3 → provide evidence for $\boxed{\text{irregular ovulation}}$

$\frac{LH}{FSH}$ LH : FSH

1 : 3

5) Obesity: Central or abdominal obesity.

Central obesity is a risk factor for DM & heart diseases. & when these diseases are present in a woman with PCOS, the clinical features are worsened (eg: anovulation, hyperandrogenis, insulin resistance)

كدة خلصنا اعراض المرض، تعالوا نشوف شوية اختبارات لازم تتعمل قبل التشخيص علشان نستبعد اي مرض تاني لاننا زي ما قلنا ان الاعراض بتاعة الـ PCOS مش ثابتة عند كل واحدة وممكن تكون بسبب امراض تانية غير الـ PCOS.

Clinical Investigations

They are lab tests made to exclude other related causes. These tests must be made before a diagnosis of PCOS is made.

Studies may include assessing concentrations of:

Prolactin ✓	To exclude:	hyperprolactinemia ✓
TSH		hypothyroidism ✓
Testosterone		Virilizing tumor
17-hydroxyprogesterone		Congenital adrenal hyperplasia.

طيب يعني ايه Virilizing tumor

It's an ovarian tumor where cells excrete excess amount of testosterone ⇒ hyperandrogenism.

ومن هنا نقدر نفهم فائدة الـ clinical investigations ليه؟

علشان ممكن واحدة تيجي للدكتور عندها اعراض ذكورية يعني Hirsutism alopecia حاجات كدة. هي عندها hyperandrogenism لكن الدكتور هيعرف منين اذا كان سببه ده PCOS ولا virilizing tumor ؟ لازم يعمل تحاليل تانية. علشان مايعملش misdiagnosis.

HOW to confirm a PCOS ?

Through a transvaginal ultrasound & finding >8 follicles per ovary that are <10mm in diameter (usually 2-8 mm)

يعني لما تكون الـ ovary الواحدة فيها اكتر من 8 follicles حجم الواحدة اقل من 10mm كده يبقى عندنا PCOS.

طيب دلوقتي احنا قلنا ان اعراض المرض بتختلف. وده بيصعب التشخيص اوي. وقبل الزمن كانوا بيستخدموا diagnostic criteria مختلفة على حسب المنظمة اللي كانت موجودة في الوقت ده.

طيب يعني ايه diagnostic criteria ؟ يعني تقول علشان تقول ان فلانة عندها PCOS لازم يكون عندها على الاقل كذا وكذا من الاعراض وممكن يكون عندها كذا او لأ. مش فهمين صح؟ (ايه كذا وكذا دي اصلا ؟؟ :))

معلش الجدول هيفهمكم ... (ان شاء الله يعني)

اقلب الصفحة ...

Diagnostic Criteria

Clinical Criteria	Proposed Definitions NIH 1990 (all marked with ×)	ESHRE/ASRM (Rotterdam) 2003 (2 of first 3 criteria and last)	AES 2006 (first criterion, ① of criteria 2 or 3, and last)
1. Hyperandrogenism or hyperandrogenemia	× لازم ده	× اتنين من التلاتة دول على الاقل	× لازم ده.
2. Oligo-ovulation or anovulation	× لازم ده	×	× واحد منهم
3. Polycystic ovaries (by ultrasound)	- ده لاء	×	×
4. Exclusion of related disorders	×. لازم ده.	× بس لازم ده.	× لازم ده

AES Androgen Excess Society; ESHRE/ASRM European Society for Human Reproduction and Embryology/ American Society for Reproductive Medicine; NIH National Institutes of Health.

كل منظمة من دول (NIH, AES & ESHRE/ASRM) عبر السنين كانت بتحط ال criteria اللي تقول ان الشخص ده عنها PCOS.

في اول واحده خالص ال NIH ، ال presence of polycystic ovaries ما كنتش من ضمن ال criteria اصلاً لان ال ultrasound ما كنتش لسه اُستخدم ساعتها في حاجه زي كدة. (عام ١٩٩٠)

كده خلصنا ال diagnosis. تعالوا نشوف حاجات جديدة

Long-term Complications

1- Impaired glucose tolerance & diabetes

2- Metabolic syndrome & Cardiovascular risk.

3- Obstructive sleep apnea.

4- Endometrial hyperplasia & Cancer.

تعالوا نتكلم عن واحد واحد...

1] Impaired Glucose Tolerance & diabetes:

Studies showed that women with PCOS have a high prevalance of:
- Impaired glucose tolerance (IGT)
- Diabetes
& - insulin resistance

ال IGT دي عبارة عن state قبل ال diabetes بيكون فيها سكر الدم عالي بس لسة مش لدرجة اننا نقول ان ال شخص عنده DM.

∴ IGT is a prediabetic state

Women with PCOS who have IGT appear to develop type 2 DM at higher rates than normal people

∴ Early Screening & diagnosis of these conditions is important for women with PCOS

طيب هنعرف ازاي ان الست عندها IGT؟ من خلال حاجتين:

1) Waist-to-Hip ratio & BMI (bodymass index)
(↑ value indicate obesity & ∴ insulin resistance & IGT)
2) Glucose tolerance test
- Fasting
& 2 hr oral (75g) test.

} To predict glucose intolerance

2] Metabolic syndrome & Cardiovascular Risk:

It's believed that insulin resistance is the primary Contributing factor to metabolic syndrome in women with PCOS with a 2 fold increased risk of Cardiovascular disease and DM

Metabolic syndrome معناها مشاكل متعلقة بال metabolism اللي في الجسم يعني زي ال lipids، الضغط، السكر.

طيب امتى نقول ان الـ ت ده عنده metabolic syndrome ؟
لما تتحقق فيه ال Criteria التالية دي:

*National cholesterol education program Criteria for Metabolic syndrome:
(NCEP)

- Three or more of the following: (الأرقام مهمة)

- Central obesity: >40 inch in ♀ / >35 inch in ♂

- Elevated triglycerides: ≥150 mg/dL or on d' Tx for this lipid abnormality

- low HDL-C: <50 mg/dL ♀ / <45 mg/dL ♂ or on drug Tx for this lipid abnormality

- Hypertension: systolic ≥135 mmHg or Diastolic ≥85 mmHg or on d' Tx

- ↑ Fasting plasma Glucose ≥100 mg/dL

∴ Metabolic Syndrome & CVS risk include

dyslipidemia, HTN, Atherosclerosis

dyslipidemia → ↓HDL, ↑TG, ↑LDL → & ↑cholesterol

3] Obstructive sleep apnea: صعوبة ف التنفس ف وضع النوم

It's the Cessation of breathing that occurs during sleep

studies indicate that the prevalance is higher in PCOS.

The cause maybe due to obesity &/or insulin resistance.

4] Endometrial hyperplasia & Cancer:

In PCOS the endometrium is exposed to the prolonged effects of estrogen (unopposed by progesteron)

∴ PCOS is a risk factor for endometrial hyperplasia.

كدة خلصنا ال Complications...

تعالوا نبدا بالعلاج بقى ...

Treatment

Treatment Goals

Primary Goals

- Treat hairsutism
- Maintain a normal endometrium
- Block androgen actions at targeted sites
- ↓ insulin resistance & hyperinsulinemia
- Reducing weight.
- Prevent long term Complications.

Secondary Goals.

- Correcting anovulation or oligovulation.
- Improve fertility.

Treatment.

Non Pharmacologic

1) Weight reduction
2) Diet
3) Excercise
4) ↓ Stress.

Pharmacologic.

1. Combined oral Contraception (COC)
2. Insulin sensitizers:
   - Metformin.
   - Thiozolidindiones.
3. Agents for hairsutism:
   - Spironolactone
   - Finasteride
4. Ovulatory inducers:
   - Clomiphen citrate

مهمة اوى التقسيمة دى علشان ، هتحلنا الدنيا.

A Non-pharmacologic Treatment:

① Weight reduction:

It's the 1st line therapy in all overweight women with PCOS

a minimum 5% weight loss has consistently demostrated restoration of regular menstrual cycle and ovulation in obese women with PCOS

بس لما حصل فقدان للوزن بنسبة ٥٪ على الأقل ، اتحسنت الدورة الشهرية والـ ovulation

② Diet:

- low saturated fat
- high in fiber from low glycemic-index-carbohydrates and protein

③ Exercise:

* AHA (american heart association): recommends 1hr daily of physical activity for weight reduction. & 30 min daily for all adults.

* ADA (american diabetes association): recomment at least 150 min per week of moderate to vigorous activity spread over at least 3 days for people with IGT
and 1hr daily of exercise for long term weight loss.

④ Reduce stress.

B] Pharmacological Treatment: (آخر المحاضرة فيه جدول مجمع كل الأدوية)

① Combined oral Contraceptives: (COC)

* Purpose:
- ✓ Regulating menstrual cycles
- ✓ Rlief from hyperandrogenic symptoms
- ✓ Reduce risk of endometrial Cancer by 50%

* Components:

- Estrogen: → -ve feed back on GnRH → ∴ Suppress LH
  - ∴ ① reduce androgen production ✓
  - ② increase hepatic production of sex hormone binding ~~protein~~ globulin SHBG
  - ∴ reduce Free testosterone ✓

طب زي ما قلنا ان زيادة الـ LH بتحفز تصنيع الـ androgens في الـ
Theca cells. وبالتالي لما اقلل الـ LH تصنيع الـ androgens هيقل

- Progestin: have variable androgenic effects so the choice of the COC is important

* Initiation:

with a formulation that contains a low or very low dose of estrogen (≤ 35 mcg ethinyl estradiol)

+ progestin with low or no androgenic effect.
  - low → ex - Desogestrel
  - norgestimate
  - no androgenic effect → ex Drospirenone

* Caution:

in those with insulin resistance, a high propability of developing type 2 DM, or abnormal lipid profile. (GR) bec COC have different effects on these metabolic disorders.

② Insulin Sensitizers:

	Metformin (Glucophage, Ciclophage)	Thiazolidindiones (Rosiglitazone, Pioglitazone)
purpose	Menstrual Cyclicity, ovulation induction, hairsutism, Acne & insulin lowerin	
Effects	Ovulation induction (better than Rosiglitazon) improves menstrual cyclicity, ovulatn & fertility in both obese & lean (non obese) patients with PCOS decrease insulin & free testosterone Concentration by 20-50% Reduce hairsutism, acne & BMI يعنى بيخسس الناس التخينة	Induce ovulation but < Metformi has moderate effect on hairsutisn
M.O.A	↓ hepatic glucose production ↓ insulin level may have direct effects on steroidogenesis	Improve insulin sensitivity at target tissue level (muscles, adiocytes) May have direct effects on steroidogenesis
Dose	500 mg TID (3times/day) 1500 850 850 1700	Rosiglitazone: 4 mg BID (2times/day Pioglitazone: 45mg PO (orally daily
S.E.	Diarrhea, N, V, bloating (انتفاخ) (transient & dose related)	edema, headache, fatigue & liver enz elevation

		Rosiglitazone have negative effect on lipid profile.
CI	women with serum Creatinine >1.4 mg/dl CHF, Metabolic acidosis	liver diseases, HF, edema patients.
DI	- Contrast agents - Cationic agents (as digoxin, aminoglycosides & trimethoprim) as they compete for tubular secretion & thus ↑ Metformin in Blood.	It's a substrate & inhibitor of CYP 2C8 so interact with any drug Met-
Pregnancy risk factor	B	C

- Pregnancy risk factor B means that studies on animals showed no fatal abnormalities on fetus but there are not enough studies made on human to confirm this

غيره بنحاول نتجنبه اثناء الحمل علشان مش متاكدين هو آمن ولا لأ

Pregnancy risk factor C means it's very dangerous on pregnancy & fetus & can't be used.

للعلم بالشرح هقولكم كل الـ grades

A : safe on animal & human
B : safe on animals but not enough studies on human.
C : SE on the ♀
D : Major abnormalities in fetus
X : fetal anomalies.

③ Agents for hairsutism.

	1- Spironolactone	2- Finasteride
Purpose	Hirsutism, Acne	Hirsutism, Acne.
M.OA	inhibit androgens from binding to androgen receptors.	5 α reductase inhibitor (type 2) ∴ decrease conversion of testosterone to the active dihydrotestosterone (DHT),
Effect	Reduce hair growth by 40-88%	Reduce hairsutism by 30%
Dose	50-100 mg BID for 6-12 months	5-7.5 mg daily for 6 months.
S.E	Hyperkalemia, polymenorrhea, headache & fatigue. (يعني بتيجي كل ٢١ يوم او اقل (مش ٢٨ يوم)	
CI	Pregnancy, renal disease & hyperkalemia	Pregnancy (Category X)
DI		CYP3A4 Substrate
Monitoring	Serum K & renal Function	
Pt counsel	avoid pregnancy as spironolact. cause possible tetratogenicity (feminizat. of male fetus) ∴ a COC is recommended with spironolactone administration to: 1) Avoid pregnancy 2) Improve hormonal & metabolic manifestations of PCOS	avoid pregnancy (GR) as this d' cause tetratogenic effect of abnormal genitalia in male fetus.

3- other agents.

- Flutamide: effective but not used due to hepatotoxicity
- Eflornithine hydrochloride: has been approved for topical use in treating facial hairsutism but has not been evaluated in women with PCOS.

④ Agents for Ovulation induction.

طبعاً مين اشهر دواء بيقوم بالدور ده ؟

Clomiphene Citrate

* **Purpose:** Induce ovulation

* **MOA:** It has an antiestrogenic effect on the hypothalamus

∴ GnRH secretion increase ⇒ increases LH & FSH production from the pituitary

The increase in FSH Causes appropriate follicle development and estrogen secretion → produce a +ve feedback on the hypothalamic-pituitary system to create LH surge & thus ovulation.

* **Dose:** initially 50 mg orally daily for 5 days started on day 5 after a spontaneous or induced menses

N.B - In pcos female

↑↑LH & ↑insuline

↓ results

++ve stimulatn of Theca Cell in ovary
To produce Testesterone

↓

△ Hirsutism & Acne

- pcos female

* insuline resistant in obese female and in
non obese one

↓

hyperinsulinemia

↓ hyperandrogenism
As ↑ testesteron

↓ metabolic
disorders

- insuline in pcos
Eeffect

↓ Direct

1 in ovary → hyper Andrgenism
2 in liver → ⊖ SHBG (sex hormone
binding globulin) w binds ē Testesterone
inBlood To ↓ its conc. so ↑↑ =

↓ inDirect

↑ Amplitude
of LH pulse

Clinician must determine if ovulation occurs with each cycle
&
if ovulation doesn't occur, dose can be increased by 50mg daily up to 150 mg daily, however:
doses > 100 mg daily for 5 days are not recommended

- Women can use Clomid for 3-4 cycles before considering another regimen if Clomid is ineffective

يعني قبل ما تقرر تغير الدواء لانه مش جايب مفعول لازم
تجربه (٣-٤) دورات علشان تتأكد فعلاً انه مش نافع

- Long term use is not recommended beyond a total of 6 cycles (GR)
  - Because of potential ovarian cancer risk.

***SE*:**
- Ovarian enlargement ✓
- Ovarian cyst formation ✓
- Hepatotoxicity ✓

.*CT*:
- Liver disease ✓
- Enlargement of ovarian cyst. ✓

in male

* hypothalmus

↓

GnRH (gonadotrapin releasing Hormon)

↓

Anterior pituiatry gland

↓ LH ↓ FSH

LH → Testis ← FSH

Testis → Testesteron (from leydig cell)

Testis → inhibin (from sertoli cell)

inhibin → FSH: -ve feed back

in Female

* hypothalmus

↓

GnRH

↓

pituaitry gland

↓ LH ↓ FSH

LH → ovary ← FSH

LH ⊕ → Theca cell

FSH ⊕ → Granullosa cell

ovary → Theca cell (outer cell)

ovary → Granullosa cell (inner cell)

Theca cell (outer cell)

cholesterol → Androstendione → Testosteron → facilitate follicale growth

Granullosa cell (inner cell)

Arromatizatn of androstendione from Theca cell → estrogen

Other agents.

Althougl Clomid is the 1st choice, It can only be used for limited number of cycles and resistance can occur.

∴ Other regimens can be used:

✓ ① Metformin (alone or in combination with Clomid)

✓ ② Dexamethasone. (in combination with Clomid)

③ Controlled ovarian stimulation with gonadotropins.

وبناءً عن المعلومات اللي عندنا لقينا انه ترتيب اختيار العلاج
هيكون كالتالي- يعني نشوف لو واحد فشل ناخد بعده ايه.

1) Combination of Clomid & Metformin, if failed:

2) Dexamethasone 0.25 mg at bed time + Clomid.

3) Ovarian Drilling & Stimulation. هنشرحها بعدين.

4) Administration of gonadotropin (disadv: ovarian hyperstimulation syndrome) OHSS.

5) In Vitro Stimulation

menstrual cycle

1 follicular phase :- (1 - 13 days) يعني من ليوم الأول لليوم ال ١٣

- Consistes of 2parts → đmenstratn (7days) in uterus
  → follicullatn in ovary
- Hormone → estrogen
- at bending of F.p đestrogen conc. ↑

هيزيد من تركيز ال phase عشان N يعمل LHsurgy

2 mid phase :- (14 - 18) يعني يوم ال ovulatn ودة بيختلف
من ست للتانية ممكن يبقى اليوم ١٤ أو ١٥ أو ١٦ أو ١٧ أو ١٨

- LH surg. ↑↑ → ovum librated from đfollicle

يعني هيحصل rupture لل follicule وتطلع ال ovum وتتحول
ال follicule إلى Corpus lutem

3 luteal phase :- من بعد يوم ال ovulatn لحد بداية cycle جديدة

- Corpus luteam release progesterone ω Thickenes đendometrium lining
- endometrium releases PGs ω cause contractn in uterus to mense

* if firtilizatn occures → embryo implanted in uterus and releasing HCG (human chorionic gonadotropin herman) This H. makes đcorpus luteam continue To release progesterone To prevent further ovulat

* if no fertilizatn → atropy in corpus luteam so no progesteren releasing → drop in progesteron level and endometrium lining is ruptured & menstruatn occures

N.B after releasing đovum in mid phase → fallopian tube

still in fallopian tube
For 3-5 days
in đbegining of tube

يعني هتفضل في اول ال tube ودة وقتها
اللي ممكن يحصل فيه Fertilizatn لمدة ٣-٥ ايام

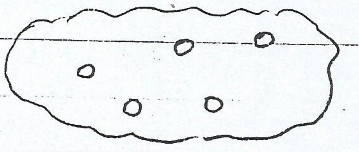
الدكتورة قالت على دوييه تانيه للتخسيس

- Orlistat
- Sibutramine } but no enough studies on its effect in PCOS.

تعالوا دلوقتي ناخد طريقة جديدة لل ovarian stimulation
دي طريقة حديثة وغريبة بس الدكتورة اتكلمت عنها تعالوا ناخد فكرة.

Ovarian Drilling.

الفكره ببساطة انهم بيعملوا فتحات (اخرام) في ال ovaries
زي بيحفروا فيها بحاجه تشبه الشنيور.
لقوا انهم لما عملوا كده حصل stimulation لل ovaries
و اتحسن شغلهم.



الصورة اللي في ال slides عاملة كده

كانه دي ال ovary وعاملين فيها اخرام
ثقوب باداه معينة كده.
تعالوا بقى نقول كلمتين بال english

Laparoscopically, (a laser fibre) or electrosurgical needle punctures the ovary 4-10 times.

Destroying part of the ovaries, restores regular ovulation cycles & dramatically lowers male hormones within days.

For patients who fail clomid & Metformin, reintiate after drilling
علشان يدي نتيجة بعد ال drilling

SE: Can cause ovarian failure if there are Complications during the procedure.

خلاص. آخر حاجة عن المعالجة. دي من ملخص مفيد اوي لأهم مراحل العلاج.

Summary

- An obese patient: 1st line weight loss.
- If Contraception is desired: 1st line COC → improve menstrual cycles & hyperandrogenism.
- Contraception not desired: Metformin → regulate menstrual cycle, hyperandrogenism & insulin resistance improvement

Other agents such as Thiazolidindiones Can be used if Metformin or COCs are Contraindicated or cause serious SE.

- If pregnancy is desired: 1st line → Clomiphene citrate.
- Other alternatives: Metformin, dexamethason, aromatase inhibitors, Gonadotropins, ovarian drilling & stimulation, invitro fertilization.

الصفحة الجاية: جدول بجمع اهم حاجات في كل دواء اخدناه، هيساعدكم على المذاكرة.